REMARKS

Amendments to the Claims

Claims 1-15 were pending.

Claim 6 has been canceled without prejudice.

Claims 1-5 and 7-12 have been amended to recite "*in vitro* method."

Claims 1, 7, 8, 11 and 12 have been amended to correct informalities.

Claims 1 and 10-12 have been amended to recite a step for determining expression levels or patterns of the genes and/or proteins. Support for this amendment can be found in the Specification, for example, at page 7, line 16 through page 8, line 19.

Claim 1 has been amended to recite "the genes and/or proteins are selected in descending order of Fisher ratio." Support for this amendment can be found in the Specification, for example, original Claim 6. Claim 1 has been also amended to recite "the expression levels or patterns of genes and/or proteins are determined by performing an assay for the gene and/or protein levels and patterns." Support for this amendment can be found in the Specification, for example, original Claim 5.

Claim 5 has been amended to recite "northern blotting, *in situ* hybridization, ribonuclease protection assay, western blot, enzyme-linked immunosorbent assay." Support for this amendment can be found in the Specification, for example, at page 7, line 16 through page 8, line 19.

No new matter has been added. Entry of these amendments is respectfully requested.

Rejection of Claims 1-12 Under 35 U.S.C. § 101

Claims 1-12 have been rejected under 35 U.S.C. § 101 as allegedly being directed to non-statutory matter.

Independent Claims 1 and 10-12 have been amended to add a step of performing an assay for determining expression levels or patterns of genes and/or proteins. Applicants note that Claims 1 and 10-12, as amended, recite a method which requires a physical transformation and are, therefore, drawn to statutory subject matter within purview of 35 U.S.C. § 101.

Rejection of Claims 1-12 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-12 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claim 1 has been rejected for lack of antecedent basis for the phrase "the statistical analyses." Claim 1 has been amended to delete "the."

Claim 6 has been rejected for lack of antecedent basis for "the Fisher ratio." Claim 6 has been canceled, rendering the rejection against Claim 6 moot.

Claims 7-9 have been rejected for lack of antecedent basis for the phrase "the number of the genes and/or protein." Claims 7 and 8 have been amended to recite "the selected genes and/or proteins in a number..." (emphasis added), rendering the rejection moot against Claims 7 and 8. Claim 9 depends from Claim 8 which now has proper antecedent basis for the phrase.

Claims 11-12 have been rejected for allegedly being indefinite for reciting "deciding." Claims 11-12 have been amended to recite "determined in step..."

Claims 11-12 have been rejected for lack of clarity in the words "data," "applying" and "all samples" in the phrase "applying the data of genes and/or proteins selected in step (b)." Claims 11-12 have been amended to delete the phrase, rendering the rejection moot against Claims 11-12.

Rejection of Claims 1-5 Under 35 U.S.C. § 102(b)

Claims 1-5 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Okabe *et al.* (Okabe *et al.*, *Cancer Res.* 61:2129-2137 (2001); hereinafter, "Okabe"). The Examiner states that: "Okabe et al teaches a method of defining the differentiation grade of a tumor with genes selected by statistical analysis using microarrays based on expression level or pattern of genes of human liver tumor tissues, wherein the differentiation grade tumor is selected from the group consisting of non-cancerous liver, pre-cancerous liver, well differentiated HCC, moderately differentiated HCC, and poorly differentiated HCC..." (Office Action at page 5, final paragraph).

Applicants disagree with the Examiner's interpretation of Okabe. Okabe teaches a method of analyzing genome-wide gene expression profiles in human hepatocellular carcinoma (HCC) by cDNA microarray assay. Okabe identified specific genes associated with HCC progression by employing the Mann-Whitney test (*see* Okabe, bridging paragraph between pages

2136-2137). Further, Okabe classified the HCC progression into two groups: (1) well-differentiated tumors (*i.e.*, Edmondson grade I); and (2) moderately-to-poorly differentiated tumors (*i.e.*, Edmondson grade II or II) (*see* Okabe at page 2136, right col., final paragraph).

Claim 1 has been amended to recite "the genes and/or proteins are selected in descending order of Fisher ratio." As noted above and acknowledged by the Examiner at page 7 of the Office Action, Okabe does not disclose statistical analysis involving the Fisher criterion. Instead, Okabe employed the Mann-Whitney test to identify genes associated with HCC progression (*see* Okabe at page 2136, right col., last paragraph). Accordingly, Claim 1, as amended, is not anticipated by Okabe.

Further, as noted above, Okabe obtained experimental results by classifying the HCC progression into two groups: (1) the well-differentiated tumors (*i.e.*, the early stage of HCC; also known as Edmondson grade I); and (2) the moderately-to-poorly differentiated tumors (*i.e.*, the later stages: also known as Edmondson grades II / III) (*see* Okabe, Figure 3A). The present invention, however, is directed to classification of HCC into five (5) groups (*i.e.*, non-cancerous liver (L0), pre-cancerous liver (L1), well-differentiated HCC (G1), moderately differentiated HCC (G2) and poorly differentiated HCC (G3)) and identification of genes involved in four (4) different transitional stages (*e.g.*, L0 to L1; L1 to G1; G1 to G2; and G2 to G3). Specifically, Claim 4 is directed to the genes that are differentially expressed during the four transitional stages (*i.e.*, between non-cancerous liver and pre-cancerous liver, pre-cancerous liver and well differentiated hepatocellular carcinoma (HCC), well differentiated HCC and moderately differentiated HCC, or moderately differentiated HCC and poorly differentiated HCC" (*see* Claim 4). Okabe simply does not disclose these methods.

For the foregoing reasons, Claims 1-5, as amended, are not anticipated by the teachings of Okabe.

Rejection of Claims 1-11 Under 35 U.S.C. § 103(a)

Claims 1-11 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Okabe *et al.* (Okabe *et al.*, *Cancer Res.* 61:2129-2137 (2001); hereinafter, "Okabe") as applied to Claims 1-5, and further in view of Adorjan *et al.* (U.S. Patent Application No. 2002/0192686 A1; hereinafter, "Adorjan"). The Examiner states that: "the invention as whole would have been

prima facie obvious to one of ordinary skill in the art at the time the invention was made absent unexpected result" (Office Action at page 9).

Applicants disagree. A *prima facie* case of obviousness has not been established because (1) the combined teachings of the prior art do not teach or suggest the present invention; (2) one of ordinary skill in the art would not have been motivated to combine the teachings of Okabe with the teachings of Adorjan to arrive at the present invention; and (3) there was no reasonable expectation of success in arriving at the present invention even if one of ordinary skill in the art endeavors to combine the teachings of Okabe with the teachings of Adorjan.

Legal Standard

In *KSR v. Teleflex*, 127 S. Ct. 1727 (2007), the Court clarified the appropriate analysis for determining obviousness under 35 U.S.C. § 103. The court restated that the Graham framework controls the analysis. Explicit findings as to (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) secondary considerations such as unexpected results should be made in the Graham analysis. The legal question of obviousness is then assessed against this factual background.

According to the Manual of Patent Examining Procedure (MPEP) at § 2141:

> The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396. Exemplary rationales that may support a conclusion of obviousness include:
>
> ....
>
> (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. MPEP § 2141, 8th Ed. Rev. 6 (July,. 2008).

The reasoning for the present rejection appears to fit best under rationale (G). To reject a claim based on this rationale, the MPEP states that:

> "…Office personnel must resolve the Graham factual inquiries. Then, Office personnel must articulate the following:
>
> (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;
>
> (2) a finding that there was reasonable expectation of success; and
>
> (3) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.
>
> The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success." *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006). If ***any*** of these findings cannot be made, then this rationale ***cannot*** be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art. (MPEP § 2143, 8th Ed. (July, 2008); emphasis added).

The Graham Analysis

1. Scope and Content of The Prior Art

Okabe

The teachings of Okabe are discussed above. Briefly, Okabe teaches a method of analyzing genome-wide gene expression profiles in human hepatocellular carcinoma (HCC) using cDNA microarray. By employing the Mann-Whitney statistical method, Okabe identified a set of genes highly associated with the HCC progression from the early stage to the later stages of HCC (*see* Okabe, bridging paragraph between pages 2136 and 2137). Okabe, however, classified the HCC progression into two specific groups: (1) the well-differentiated tumor group (*i.e.*, the early stage; Edmondson grade I); and (2) the moderately-to-poorly differentiated tumor group (*i.e.*, the later stage; Edmondson grades II and III) (*see* Okabe at page 2136, right col., final paragraph; Figure 3A).

Adorjan

Adorjan teaches a method for identifying an epigenetic feature (*i.e.*, DNA methylation) between two particular types of cancer: (1) acute myeloid leukemia (AML); and (2) acute lymphobalastic leukemia (ALL). To identify DNA methylation profiles highly associated with AML and ALL from a large scale genome-wide methylation data, Adorjan teaches various types of statistical selection criteria, including the Fisher criterion (*see* Adorjan, paragraphs [104] and [105]).

2. Differences Between the Prior Art and the Present Claims At Issue

First, Okabe classified tumor samples into two specific groups: (1) the well-differentiated tumor group; and (2) the moderately-to-poorly differentiated tumor group and identified genes highly associated with cancer progression from the well-differentiated tumor stage to the moderately-to-poorly differentiated tumor stage. Unlike Okabe, the present invention classifies the HCC progression into five distinct stages: *i.e.*, noncancerous liver (L0), pre-cancerous liver (L1), well-differentiated HCC (G1), moderately differentiated HCC (G2) and poorly differentiated HCC (G3); and identifies genes whose expressions are significantly altered during the four (4) distinct transitional stages (*e.g.*, L0 to L1; L1 to G1; G1 to G2; and G2 to G3).

Second, Okabe teaches the Mann-Whitney test for identification of the genes whose expressions are significantly altered between the early state and the late stages of HCC as discussed above, whereas the present invention employs the Fisher criterion to identify genes and/or proteins whose expressions are significantly altered during the four distinct transitional stages of HCC.

Third, Adorjan teaches the Fisher criterion to identify unique DNA methylation profiles of the two distinct types of cancer (*i.e.*, AML and ALL), whereas the present invention employs the Fisher criterion to identify genes significantly associated with progression of a particular cancer (*e.g.*, HCC) divided into the five (5) distinct grades.

Neither Okabe nor Adorjan teaches or suggests that the Fisher criterion can be employed to determine differences in gene expression profiles in five different grades of cancer.

3. The Level of Ordinary Skill In The Art

The level of one of ordinary skill in the art at the time of the invention was the level of ordinary skill in molecular biology and bioinformatics specialized in analyzing genome-wide expression profiles and performing microarray assays in an academic or industrial setting.

A Prima Facie Case of Obviousness Has Not Been Established

A *prima facie* case of obviousness has not been established because: (1) the combined references cited do not teach or suggest an *in vitro* method of defining the differentiation grade of a tumor into five different classes; and (2) one of ordinary skill in the art would not have been motivated to combine the teachings of Okabe with the teachings of Adorjan; and (3) there is no reasonable expectation of success in arriving at the present invention.

1. The combined teachings of the prior art references do not teach or suggest the present invention

Neither Okabe nor Adorjan teaches or suggests a method of involving classification of HCC into five (5) distinct groups as in the present invention. As noted above, Okabe merely identifies genes whose expressions are significantly altered between two stages (*i.e.*, well-differentiated HCC and moderately-to-poorly differentiated HCC) (*see* Figure 3A). However, the present invention classifies the HCC progression into five (5) distinct stages: *i.e.*, noncancerous liver (L0), pre-cancerous liver (L1), well-differentiated HCC (G1), moderately differentiated HCC (G2) and poorly differentiated HCC (G3); involving four (4) distinct transitional stages (*e.g.*, L0 to L1; L1 to G1; G1 to G2; and G2 to G3).

2. No Motivation to Combine the Teachings of Okabe with the Teachings of Adorjan

One of ordinary skill in the art would not have been motivated to combine or modify the teachings of Okabe and Adorjan to arrive at the present invention because the skilled artisan reading Okabe would not look to the teachings of Adorjan. Okabe analyzed the gene expression data by using the Mann-Whitney test and successfully identified a total of 321 genes whose expressions are significantly altered from the early stage of HCC ("the well-differentiated tumor group") to the late stages of HCC ("the moderately-to-poorly differentiated tumor group") (*see* Okabe at page 2136, right col.; Figure 3A). The teachings of Okabe do not motivate one of ordinary skill in the art to look to the teachings of Adorjan to substitute the Mann-Whitney test

of Okabe with the Fisher criterion of Adorjan because the Mann-Whitney test is one of the best-known non-parametric statistical methods of measuring the significance of two given samples. Using the Mann-Whitney test, Okabe successfully identified 321 specific genes highly associated with the transition from the early stage to the late stage of HCC. In the teachings of Okabe, the usage of the Mann-Whitney test appears proper and complete (*see* Okabe, Figure 3A). One of ordinary skill in the art would not have been motivated to look to the teachings of Adorjan.

Adorjan does not motivate one of ordinary skill in the art to employ the Fisher ratio in place of the Mann-Whitney test as taught in Okabe. Nor does it provide any inference that the Fisher criterion is superior to the Mann-Whitney test. One of ordinary skill in the art would not have been motivated to combined the teachings of Okabe and Adorjan to arrive at the present invention.

In addition, one of ordinary skill in the art would not have been motivated to modify the teachings of Okabe with the teachings of Adorjan to arrive at the present invention because the references of record provide no teaching, suggestion or inference for a method of defining the differentiation grade of a tumor into five (5) distinct stages as in the present invention.

Therefore, a *prima facie* case of obviousness has not been established.

3. No Reasonable Expectation of Success

To conclude that a claim is obvious in view of a prior art, a reasonable expectation of success is required (*see* MPEP § 2143). One of ordinary skill in the art at the time the invention was made would not have had a reasonable expectation of success in arriving at the present invention because Okabe, as discussed above, used a combined category of the later stages of HCC termed as "the moderately-to-poorly differentiated tumor group" and made only one comparison of gene expression levels between the early stage of HCC ("the well-differentiated tumor group) and the later stage of HCC ("the moderately-to-poorly differentiated tumor group"). In contrast, the present application teaches and successfully exemplifies the use of five distinct HCC groups as elaborated above. Accordingly, even if a skilled artisan endeavors to combine the teachings of Okabe with the teachings of Adorjan, one of ordinary skill in the art would not have been able to arrive at the claimed invention with a reasonable expectation of success, absent: (1) a specific knowledge that the HCC progression can be classified into five

distinct groups as in present invention; and (2) empirical genome-wide expression data for each of the five groups.

Further, independent Claims 10-12 specifically recites a comparison step between non-cancerous liver and pre-cancerous liver, pre-cancerous liver and well differentiated hepatocellular carcinoma (HCC), well differentiated HCC and moderately differentiated HCC, or moderately differentiated HCC and poorly differentiated HCC. The Examiner is reminded that "all words in a claim must be considered in judging the patentability of that claim against the prior art." MPEP § 2143.03.

For the foregoing reasons, a *prima facie* case of obviousness has not been established.

The Present Invention Achieves Unexpected Results

Assuming, *arguendo*, that a *prima facie* case has been established, the *prima facie* case is effectively overcome because the present invention achieves unexpected results. According to the MPEP § 2141, "[o]ffice personnel should consider all rebuttal evidence that is timely presented by the applicants when reevaluating any obviousness determination. Rebuttal evidence may include evidence of secondary considerations, such as commercial success, long felt but unsolved needs, [and] failure of others (*Graham v. John Deere Co.*, 383 U.S. at 17, 148 USPQ at 467), and may also include evidence of unexpected results." *Id.* (emphasis added).

It is noted that genes not identified by Okabe were identified by the present invention. The top 5 genes associated with the transition between G1 and G2, for example, which were identified by descending order of the Fisher ratio as shown in TABLE 5 (G1-G2 analysis) of the present invention were not identified by Okabe (*see* Okabe, Figure 3). For example, the present invention demonstrates successful identification of OAS2, STAT1, PSME1, ISGF3G and PSMB9 that are significantly down-regulated during the transition between G1 and G2 (*see* Example 10; Table 5). None of these genes were reported by Okabe as the genes that are differentially regulated between G1 and G2/G3 (*see* Okabe, Figure 3A). Applicants respectfully note that these genes identified by the present invention are known to be associated with prostate cancer tumor progression (*see* the Specification at page 27, line 32 through page 28, line 9), indicating a correlation of cancer progress in HCC and prostate cancer. The present invention clearly achieves unexpected results and provides expression profiles that are superior to the prior art available at the time the invention was made.

In addition, the present invention also provides a method for better predicting the grade of an unknown tumor sample. By specifically classifying HCC progression into five distinct groups, *i.e.*, L0 (the non-cancerous group), L1 (pre-cancerous group), G1 (Edmondson Group I), G2 (Edmondson Group II) and G3 (Edmondson Group III), the present invention provides more refined and precise prediction or diagnosis for a possible tumor grade of HCC.

In sum, a *prima facie* case of obviousness has not been established because one of ordinary skill in the art would not have been motivated to combine or modify the teachings of Okabe and Adorjan to arrive at the claimed invention. Even if the referenced are combined, one of ordinary skill in the art would not have had a reasonable expectation of success in arriving at the present invention. Finally, the present invention overcomes any obviousness because it achieves unexpected results. Withdrawal and reconsideration of the rejection are respectfully requested.

Rejection of Claims 1-12 Under 35 U.S.C. § 103(a)

Claims 1-12 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Okabe *et al.* (Okabe *et al.*, *Cancer Research.* 61:2129-2137 (2001); hereinafter, "Okabe") in view of Adorjan *et al.* (U.S. Patent Application No. 2002/0192686 A1; hereinafter, "Adorjan") as applied to Claims 1-11 above, and further in view of Bloch *et al.* (U.S. Patent No. 6,728,642 B2; hereinafter, "Bloch").

The teachings of Okabe and Adorjan are discussed above.

Bloch teaches how to use the minimum distance classifier and also teaches how to illustrate classified genes into self-organized maps.

The deficiencies of the combined teachings in Okabe and Adorjan are discussed above. The teachings of Bloch drawn to the minimum distance classifier simply do not compensate for the deficiencies of the combined teachings of Okabe and Adorjan.

For the foregoing reasons, Claim 1-12, as amended, are not *prima facie* obvious over the combined teachings of Okabe, Adorjan and Bloch. Withdrawal and reconsideration of the rejection are respectfully requested.

Double Patenting

Claims 1-12 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 37, 40-46, 48-53 and 57-68 of U.S. Patent Application No. 11/484,664.

Applicants respectfully note that U.S. Patent Application No. 11/484,664 cited in the Office Action (*see* Office Action at page 11) is a patent application (now U.S. Patent No. 7,566,933) that has no common subject matter with the present application. Further, Claims 37, 40-46, 48-53 and 57-68 recited in the Office Action do not exist in the cited patent application. Applicants request for clarification of the statement in the Office Action.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner disagrees but feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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